

# Pharmacological Treatment of Bladder Dysfunction

## Introduction

- Functional Anatomy
- Normal Storage and Voiding Reflexes
- Neurophysiology of Bladder Contraction and Relaxation
- Pharmacological Treatment/ Drug Groups
  - Oral Therapy
  - Intravesical Therapy

## Functional Bladder Anatomy

### Bladder Body

- Above ureteric orifices
- 3 layers – adventitia, smooth muscle, and urothelium.
- Haphazard arrangement of smooth muscle myofibrils. Acts as functional syncytium. No specific gap junctions, but 'areas of close proximity'
- 2 main populations of receptors, cholinergic (muscarinic) and adrenergic
- Muscarinic subtypes M<sub>2</sub> and M<sub>3</sub> in bladder smooth muscle. M<sub>2</sub> 80% population, but M<sub>3</sub> functionally important
- Adrenergic subtypes β<sub>1</sub> and β<sub>2</sub>
- Afferent nociceptive impulses via pelvic nerves to S<sub>2/3/4</sub>

### Bladder Base

- Trigone and bladder neck
- 2 distinct layers of smooth muscle. Superior thin layer of longitudinal alpha-adrenergic smooth muscle contiguous with ureters. Passes down to the verumontanum in male and proximal urethra in female.
- Deep layer of smooth muscle merges with detrusor. Relative absence of M and β receptors.
- Afferent impulses from trigone relay information about stretch via hypogastric nerves (T<sub>10</sub>-L<sub>2</sub>)

### Pre-Prostatic Sphincter (Male)

- Circumferential collar of alpha-adrenergic smooth muscle surrounding bladder neck. Merges with prostatic capsule.
- Alpha 1A predominant receptor subtype
- With alpha-adrenergic peri-prostatic smooth muscle forms reproductive unit important at orgasm.
- Minimal importance in preserving continence.

## Urethral Sphincter Mechanism

- Circular striated muscle horseshoe (rhabdosphincter) around inner longitudinal smooth muscle (internal urethral sphincter)
- Re-inforcement in times of emergency by pubourethral sling (levator ani). Somatic via pudendal nerve S2/3/4
- Rhabdosphincter
  - Small fibres, high numbers of mitochondria, and packed with lipid droplets. Likely to be major component in maintaining continence
  - Somatic innervation – S2/3 Onuf's nucleus via pelvic nerves
  - Cholinergic nicotinic receptors
- Mechanism for maintenance of tone controversial. Neuromuscular blockade (striated muscle) reduces urethral pressure at sphincter by only 40% suggesting smooth muscle component plays a part important.
- Alpha-blockade (sympathetic smooth muscle) reduce urethral sphincter pressure by only approx 30%
- **Therefore continence likely to result from a combination of intrinsic striated muscle tone and sympathetic induced smooth muscle tone.** There may also be a role for NANC transmission (Serotonin/ GABA)
- Parasympathetic system has no role in maintaining EUS tone
- Parasympathetic stimulation acts to inhibit sympathetic induced tone, and to cause relaxation of urethral smooth muscle, probably by release of NO, an inhibitory neurotransmitter.

## **Storage and Voiding**

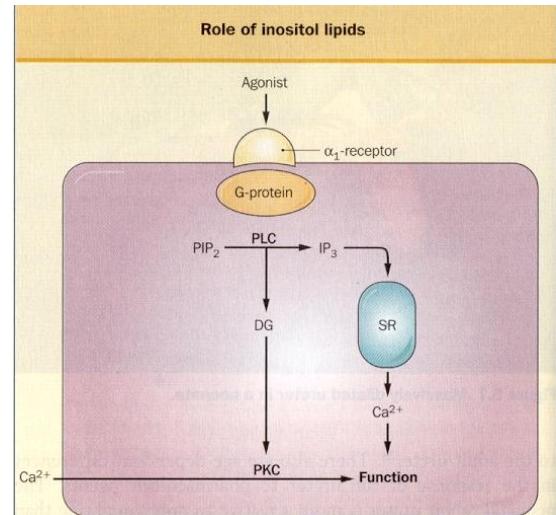
**Table 23–4. REFLEXES TO THE LOWER URINARY TRACT**

Afferent Pathway	Efferent Pathways	Central Pathway
<b>Urine Storage</b> Low level vesical afferent activity (pelvic nerve)	1. External sphincter contraction (somatic nerves) 2. Internal sphincter contraction (sympathetic nerves) 3. Detrusor inhibition (sympathetic nerves) 4. Ganglionic inhibition (sympathetic nerves) 5. Sacral parasympathetic outflow inactive	Spinal reflexes
<b>Micturition</b> High level vesical afferent activity (pelvic nerve)	1. Inhibition of external sphincter activity 2. Inhibition of sympathetic outflow 3. Activation of parasympathetic outflow to the bladder 4. Activation of parasympathetic outflow to the urethra	Spinobulbospinal

## Neurophysiology

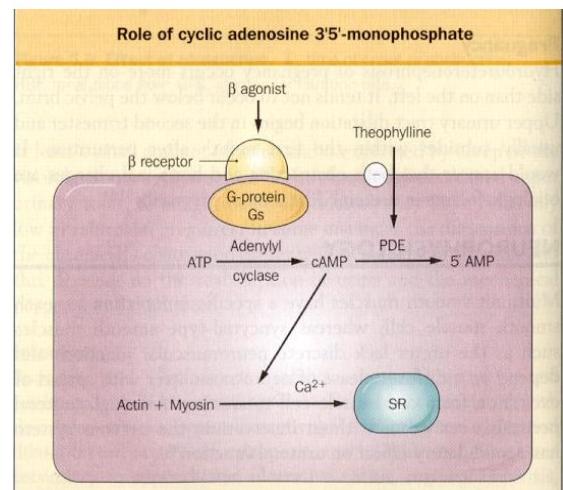
### Smooth muscle contraction

- Mediated by activation of M3 receptors (bladder) and  $\alpha_1$  adrenoceptors (urethra)  
Common final pathway
- Receptor activation results in activation of phospholipase C, via a guanine nucleotide regulatory 'G protein'.
- Phospholipase C hydrolyses PIP<sub>2</sub> to inositol triphosphate (IP<sub>3</sub>) and diacylglycerol (DG).  
DG opens gated calcium channels, and IP<sub>3</sub> stimulates calcium release from sarcoplasmic reticulum
- Increased calcium results in contraction via calmodulin- MLCK, actin and myosin.



### Smooth muscle relaxation

- 2 similar mechanisms mediated by cyclic AMP and cGMP
- Cyclic AMP
  - Beta adrenoceptor mediated relaxation of detrusor
  - Stimulatory G protein activates adenylyl cyclase, resulting in the formation of cyclic AMP from ATP
  - cAMP drives calcium back into sarcoplasmic reticulum, reducing cytosolic stores and facilitating relaxation
- Cyclic GMP
  - Parasympathetic mediated relaxation of urethral smooth muscle
  - Nitric oxide synthase acts on L-arginine to produce NO and citrulline
  - NO diffuses into cell to activate guanylyl cyclase to produce cGMP.
  - cGMP acts in a similar way to cAMP causing smooth muscle relaxation.



## Pharmacology

Table 23–5. DRUGS WITH BLADDER ACTION

Classification	Examples	Pharmacologic Action
Anticholinergic agents	Atropine Glycopyrrrolate Oxybutynin Propantheline Tolterodine	Inhibit muscarinic receptors, thus reducing the response to cholinergic stimulation. Used to reduce pressure during bladder filling and for the treatment of unstable bladder contractions.
Smooth muscle relaxants	Dicyclomine Flavoxata	Direct smooth muscle relaxation reduces intravesical pressure during filling and reduces severity and presence of unstable bladder contractions. Most of these agents have some degree of anticholinergic action.
Calcium antagonists	Diltiazem Nifedipine Verapamil	Used in the treatment of unstable bladder contractions to reduce the magnitude of the spikes by reducing the entrance of calcium during an action potential.
Potassium channel openers	Cromakalim Pinacidil	Act to increase the membrane potential and thus reduce the myogenic initiation of unstable bladder contractions.
Prostaglandin synthesis inhibitors	Flurbiprofen	Prostaglandins have been implicated in increased smooth muscle tone and in the induction of spontaneous activity. Inhibition of prostaglandin synthesis could promote relaxation of the bladder during filling and decrease spontaneous activity of the bladder.
$\beta$ -Adrenergic agonists	Isoproterenol Terbutaline	Stimulation of $\beta$ receptors induces relaxation of the bladder body, resulting in a decrease in intravesical pressure during filling.
Tricyclic antidepressants	Amitriptyline Imipramine	These agents have anticholinergic, direct smooth muscle relaxant, and norepinephrine-reuptake inhibition properties.
$\alpha$ -Adrenergic agonists	Ephedrine Phenylpropanolamine Midodrine Pseudoephedrine	Increase urethral tone and closure pressure by direct stimulation of $\alpha$ -adrenergic receptors.
Afferent nerve inhibitors	DMSO Capsaicin Resiniferatoxin	Reduce the sensory input from bladder and thereby increase bladder capacity and reduce bladder instability.
Estrogen	Estradiol	Direct application to the vagina or oral therapy may increase the thickness of the urothelial mucosa, making a better seal and reducing the incidence of incontinence. Other actions may include increasing adrenergic effects on the urethra and increasing blood flow.

DMSO, dimethyl sulfoxide.

## Anticholinergics

### Indications

- Detrusor instability
- Incontinence
- Urgency
- Catheter induced bladder spasm

### Mechanism of action

- Blockage of muscarinic acetylcholine receptors to inhibit unstable detrusor contraction

### Side effects

- **Dry mouth**
- Constipation

- Sweating
- Blurred vision
- Tachycardia
- Urinary retention

#### NHS Available Drugs

- Classic antimuscarinics (propantheline, glycopyrrolate, atropine, etc)
  - Non-selective M antagonists
  - Poor side effect profiles
- **Oxybutynin**
  - Some selectivity for M1 and M3 receptor subtypes
  - Additional direct smooth muscle relaxant, probably via calcium channel blockade
  - Potent antimuscarinic but weak direct smooth muscle relaxant (500x less)
  - Extensive first pass metabolism. Metabolite (desethoxybutynin) more potent but more side effects
  - Multiple randomised trials have confirmed efficacy but at expense of compliance rates due to side effect profiles
  - OxybutyninXL comparable efficacy to immediate release but improved tolerability in multi-centre trial (Andersson 1999)
- Tolterodine
  - Not receptor specific but greater affinity for bladder vs. salivary gland
  - Most commonly prescribed drug in US
  - Efficacy of immediate release tolterodine vs. oxybutynin similar but tolterodine has improves side effect profile (Chapple 2000)
  - Comparison of TolterodineXL (4mg od) vs immediate release (2mg bd) resulted in 18% reduction in urge incontinence and 23% lower side effects (Van Kerrebroek 2001)
- Trospium
  - Non-selective M antagonist with some anti-nicotinic effects in vitro
  - Similar efficacy to oxybutynin but more favourable side-effect profile
  - Further studies required
- Flavoxate
  - Initially thought to be weak anticholinergic but in fact acts as calcium channel blocker and PDE inhibitor
  - Good quality side-effect profile but questionable efficacy in DI and hyperreflexia
- Darifenacin (Non-NHS)
  - Highly selective M3 receptor antagonist
  - Animal studies indicate predilection for bladder vs. salivary gland
  - Too few studies at present to recommend routine usage
  - Unlicensed at present
- Solifenacin (Vesicare)
  - M3 receptor antagonist

- STAR trial Chris Chapple – need to review

### Beta-Agonists

- Animal studies show strong dose-related effect of  $\beta_2$  agonists on bladder body, but not on bladder base or urethra.
- Direct stimulation of  $\beta$  receptors induces adenylyl cyclase mediated smooth muscle relaxation
- No effect reported on normal human bladder but **terbutaline reported to be efficacious in small case series in patients with DI and urge incontinence.**
- Troublesome tachycardia, palpitations, and tremor
- Currently not recommended

### Alpha-Blockers

- Whilst alpha-adrenergic responses not present in normal detrusor, they appear to develop in bladder dysfunction due to spinal injury and bladder outflow obstruction.
- Spinal injury/ bladder denervation associated with urethral supersensitivity to  $\alpha$ -adrenergic stimulation, increased outflow resistance and decreased compliance.
- A reduction in bladder compliance, contraction, and filling pressures, can be achieved with alpha-blockers.
- Alpha-blockers well-recognised to reduce irritative symptoms in BOO, but quality randomised trials in DI/ detrusor hyperreflexia lacking. Not currently licensed for this indication.

### Calcium Channel Blockers

- Antagonise muscarinic-mediated calcium channel opening and intracellular calcium release
- Known to be a potent mechanism for detrusor smooth muscle relaxation
- Calcium channels not bladder specific however
- Side-effects
  - hypotension, facial flushing, headache, dizziness, abdominal discomfort, constipation, nausea, rash, weakness, and palpitations
- Available information at suggests that **oral administration of calcium channel blockers ineffective for treatment of DI**. There may be a role for intravesical therapy or synergistically with anticholinergics
- Terodilane has combined anticholinergic and calcium channel blocking properties, and confirmed efficacy, but withdrawn due to unacceptable cardiotoxicity in elderly and with antidepressants/antipsychotics.

### Tricyclic Antidepressants

- Extensively studied in CNS – findings extrapolated to LUT

- Mechanisms of action
  - Central and peripheral anticholinergic effects
  - Serotonin and noradrenaline reuptake inhibitors
  - Sedatives
- Significant side-effect profiles
  - Predominantly anticholinergic
  - Allergic – rash, abnormal LFTs, agranulocytosis
  - CNS – weakness, fatigue, parkinsonism, UL tremor, mania, psychosis
  - Other – Impotence, postural hypotension, arrhythmias
- Imipramine
  - Weak antimuscarinic effects on bladder BUT strong direct inhibitory effects on bladder smooth muscle. ? mechanism – not cholinergic or adrenergic ? Serotonergic
  - Clinical trials in 1970s + 1980s confirm efficacy but use declined.
  - Well known efficacy in childhood enuresis. ? mechanism

## Other Drugs

- Duloxetine
  - Selective serotonin and noradrenaline re-uptake inhibitor
  - In animal models acts to depress bladder contractility (serotonergic) and increase EUS tone (serotonergic and adrenergic)
  - Recent multi-centre RCT (n = 450) reports good efficacy for 40mg bd of duloxetine in reducing SUI frequency. Main side-effect = mild nausea 17% (Millard BJUI 2004)
- Baclofen
  - GABA<sub>A</sub> agonist
  - Depresses motorneurones and interneurones in spinal cord
  - Appears to work in DSD by relaxing EUS but also reported to reduce frequency and incontinence in idiopathic DI
  - Few quality randomised trials however (nothing since 1993)
- No evidence for Potassium channel openers or Prostaglandin inhibitors in bladder instability

## Intravesical Agents

- Reduction in afferent inputs decrease likelihood of abnormal micturition reflex
- Capsaicin
  - Acts on vanilloid receptor subtype 1 found on polymodal nociceptors
  - Receptor activation opens calcium/sodium channels – depolarisation of c-fibres
  - Repeat stimulation desensitises and inactivates sensory neurones after primary 'flare'

SCOVILLE SCALE	
In 1912 Wilbur Scoville developed his now famous method to chart the comparative heat of different chillies ( <i>J. Am. Pharm. Assoc.</i> 1912; 1:453-4). The greater number of Scoville Units, the hotter the chilli. For example:	
Bell Pepper.....	0 Scoville Units (SU)
Peperoncini, Cherry Pepper .....	100–500
New Mexico, Aji Panca .....	500–1,000
Ancho, Passila, Espanola .....	1,000–1,500
Sandia, Rocotoillo, Cascabel, Poblano .....	1,500–2,500
Jalapeno, Mirasol .....	2,500–5,000
Chilcostle, Louisiana Hot .....	5,000–10,000
de Arbol, Serrano, Japones .....	10,000–30,000
Piquin, Aji, Cayenne, Tabasco .....	30,000–50,000
Chilepin, Tepin .....	50,000–80,000
Habanero, Scotch Bonnet .....	80,000–300,000
Pure Capsaicin.....	16,000,000

*This can only be a rough guide, since the heat of chillies can vary from pepper to pepper.*

- 1-2mM single installation clinically effective in small study groups with neuropathic bladders
  - **Problematic side-effects**, including burning, bleed, and autonomic dysreflexia. Pain abolished with LA pre-treatment
  - DeRidder (2000) reported 84% improvement in meta-analysis of 115 patients
- Resiniferatoxin
  - Vanilloid from *Euphorbia resinifera*
  - **1000x more potent than capsaicin without 'flare'**
  - Highly promising. Study of 27 patients with MS showed mean bladder capacity increase of 259ml after 1 month.
- DMSO effective in interstitial cystitis but not in DI/ DH